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THERAPEUTIC COMPOSITION USEFUL AS TOPICAL DIGESTIVE

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Description

The present invention concerns a therapeutic composition which has thixotropic coating properties and which is useful as a topical digestive, notably in the field of gastric coatings.

According to the invention, a therapeutic composition is described which consists of the synergistic association of at least two mineral substance, useful as topical digestive and offering the advantage that they can be administered in the case of diabetes or a dietary regimen.

A proprietary drug is known, notably from the Dictionnaire Vidal, 55th edition (OVP, Paris, 1979), pp. 659-660, which contains, in powdered form, 2 wt% TiO_2 and 95 wt% antacid products and, in the form of a tablet, 0.63 wt% TiO_2 and 98.10 wt% antacid products. The TiO_2 used in this proprietary drug is presented as a protective agent of the gastric mucosa.

It has been discovered, surprisingly, that in order to have a good coating effect over a long period of time, and excellent thixotropic properties, it is important that the TiO_2 content in the composition be larger than or equal to 5 wt% with reference to the weight of said composition.

The composition according to the invention is applicable, in particular, in the treatment and the prevention of gastric ulcers, esophagitis, hiatal hernia, gastroesophageal reflux, gastritis, duodenal ulcers, duodenitis, enteritis, enterocolitis, colitis, colonopathy, rectitis and acute diarrhea of bacterial or viral origin, both in adults and in children. It promotes the regeneration of the mucosa and, because of its coating properties, allows cicatrization of the epithelium that it protects to occur.

This composition is characterized in that it contains, in association with a physiologicaly acceptable excipient, at least two mineral substances as active ingredients:

A--titanium oxide as a coating means and suspended thixotrope, and

B--an antacid means, chosen, for example, from the group consisting of $CaCO_3$, MgO, $MgCO_3$, Al_2O_3, $Al(OH)_3$, aluminum phsophate [sic; phosphate] and $BaCO_3$,

the ratio by weight of the means A and B being between (1:10) and (10:1), and the mean content of A being greater than or equal to 5 wt% with respect to the weight of said composition.

At the level of the stomach, the means A acts mechanically as a coating agent, isolating the mucosa from the stomach contents, and therapeutically as an agent which promotes the regeneration of the mucosa and allows the cicatrization of the

epithelium to occur, whereas the means B intervenes by its antacid effect. The means A and B act in the same mann r on the other mucosas of the digestive system. The preferred means A is the anatase variety of TiO_2, and the preferred means B is $CaCO_3$. The preferred ratio by weight of A/B is between (1:1 [sic; 1:10]) and (10:1).

Advantageously the therapeutic composition according to the invention can also contain a mineral filler C or a gelling agent D. Preferably, a composition containing the four means A, B, C and D is used.

The means C is an agent which promotes the intestinal transit and which has a synergistic effect with the combination of A and B on the coating and protecting effect, on the one hand, and the thixotropic properties, on the other hand. The ratio by weight of C/A is between (1:90) and (1:10) and advantageously between (1:50) and (1:20). Advantageously, the means C will be chosen from the group consisting of clay, bentonite and montmorillonite. In this regard, it has been observed that talc and mica (substances which could be of interest because of their lubricating property) are not suitable as means C, when their use in the composition according to the invention decreases the thixotropic properties.

The gelling agent D that is described is advantageously chosen from the group consisting of the pectins and the cellulose derivatives, notably the cellulose ethers and carboxymethylcellulose. The preferred ratio by weight D/A is between (1:50) and (1:20).

The composition according to the invention can be administered in human and veterinary therapy, notably in the form

of tablets, capsules, aqueous suspensions and gels, for oral administration and, possibly, in the form of suppositories, for rectal administration.

Other advantages and characteristics of the invention will become clear after a reading of the following examples which in no way are limiting, rather they are given for illustration only. Example 1 below constitutes the best embodiment variant.

Example 1

A composition useful as topical digestive is prepared from the means A-D and the excipients given in the following formulation:

Formulation 1

Mean A: TiO_2 (anatase)	9	g
Mean B: $CaCO_3$	3	g
Mean C: clay	0.25	g
Mean D: carboxymethylcellulose	0.30	g
Excipients:		
glycerin	20	g
sodium saccharinate	0.025	g
methyl-p-hydroxybenzoate	0.13	g
propyl-p-hydroxybenzoate	0.02	g
lemon flavor	0.08	g
raspberry flavor	0.168	g
color (Red 2G at 1 wt%/volume)	0.2	g
distilled water	100	g

Into the distilled water, the following ar successively introduced (i) the sodium saccharinate, (ii) the methyl-para-hydroxybenzoate followed by the propyl-para-hydroxybenzoate, (iii) the glycerin, (iv) the means D, CMC, (v) the means C, clay marketed under the name of "Veegum HV," (vi) the means B, calcium carbonate, (vii) the means A, titanium oxide, (viii) the lemon flavor, marketed under the name of "Givaudan 60863-76," the cherry flavor, marketed under the name of "IFF 6K 103," and the dye, and then (ix) distilled water in a sufficient quantity to obtain a composition having a total weight of 100 g, which is notably presented in the form of a gel.

Example 2

Using the protocol described in Example 1, a composition useful as a topical digestive according to the invention is prepared in which TiO_2 (means A), $CaCO_3$ (means B), bentonite (means C) and pectin (means D) are in the following ratio by weight: (30:30:1:1).

Example 3

As indicated in Example 2, a composition according to the invention, useful as a topical digestive, is prepared in which the ratio by weight of TiO_2, $CaCO_3$, clay and CMC is (90:20:2:3).

Examples 4-9

Proc eding as indicated in Example 1, compositions (Examples 4-9) according to the invention, useful as topical digestives, are prepared by replacing in the formulation the 3 g $CaCO_3$ by 4 g MgO, 10 g aluminum phosphate, 5 g Al_2O_3, 4 g $MgCO_3$, 4 g $BaCO_3$ and, respectively, 5 g $Al(OH)_3$.

Example 10

According to the protocol described in Example 1, but using in the formulation a quantity of 5 g TiO_2 instead of 9 g, a composition useful as topical digestive and having an excellent coating effect is prepared (see Table I below).

Comparative example

According to the protocol described in Example 1, but using in the formulation a quantity of 4.9 g TiO_2 instead of 9 g, a composition (hereafter called A3) is obtained which does not have a good coating effect 4 h after administration (see Table I below).

A part of the tests that were performed with compositions according to the invention to determine their coating effect is summarized below.

The principle of determining the coating effect is based on the knowledge that, in rats after prolonged fasting, the administration of a topical digestive as a gastric coating results in a deposition of the medication which can be evaluated

after sacrificing the animals and xposing the stomachs. The animals were sacrificed at two different measuring times: 0.5 h and 4 h after administration:

110 male Wistar rats, each weighing 300 g, are fasted for 48 h, with drinking water ad libitum, then they are distributed into groups, as follows: 2 control groups (5 animals each) and two groups of 10 animals each for each tested composition, that is Examples 1 and 10 according to the invention, with a reference topical digestive (A1) containing in its formulation 55 wt% colloidal aluminum phosphate, the proprietary drug (A2) described in the above-mentioned Dictionnaire Vidal, and the comparative example (A3).

All the animals receive 5 mL water by gastric intubation, 30 min before the administration of the compositions to be studied to eliminate any residual gastric contents. Said compositions are administrated by gastric intubation in a volume of 1 mL per 100 g body weight, control groups being treated under the same conditions with ordinary water. The animals are sacrificed 0.5 h and 4 h after the administration.

After the sacrificing (breaking of the neck), the stomachs are removed and cut open along the long curvature. They are cleaned of any excess composition (case of measurement after 0.5 h) by 5 successive immersions in an isotonic aqueous solution of NaCl. The stomachs are then exposed and the coating effect is evaluated by the intensity of the deposit of medication at the level of the rumen (R) and at the level of the glandular part (G) of the stomach, using the following ranking:

0: absence of deposits,

1: occasional deposits,

2: clearly visible deposits,

3: large deposits,

4: generalized deposits.

The results listed in Table I below (which gives the sums of the individual scores using the above-described ranking) show that: (i) after 0.5 h, the composition of Examples 1 and 10 and the reference composition A1 have approximately the same coating effect (each composition being still in part in the stomach), and (ii) after 4 h, the compositions according to Examples 1 and 10 have a greater coating effect than that of the compositions A1, A2 and A3.

Table I. Coating effect

Composition	Teneur en TiO_2 (1)	0,5 h après administration (2)			4 h après administration (2)		
		R	G	R+G	R	G	R+G
Eau (témoin) (3)	0%	0	0	0	0	0	0
A1	0%	35	18	53	9	8	17
A2	2%	29	16	45	8	6	14
A3	4,9%	30	17	47	8	7	15
Ex 1	9%	31	21	52	13	15	28
Ex 10	5%	31	20	51	13	14	27

(4) Notes:

R: rumen

G: partie glandulaire

R+G: somme de R et G

A1: composition de référence ayant la formulation suivante pour 100 g:

- phosphate d'aluminium colloïdal	55	g
- parahydroxybenzoate de méthyle	0,11	g
- parahydroxybenzoate de propyle	0,04	g
- acide sorbique	0,15	g
- saccharose	15	g
- autre excipients: pectine, agar-agar, essence d'orange et eau, q.s.p.	100	g

A2: composition de référence décrite dans le Dictionnaire Vidal susvisé et ayant la formulation suivante pour 100 g (présentation poudre):

- $NaHCO_3$	52	g
- $CaCO_3$	41	g
- $Ca_3(PO_4)_2$	2	g
- $Mg(OH)_2$	3	g
- TiO_2	2	g

A3: exemple comparatif

Key: 1 TiO_2 content
2 After administration
3 Water (control)
4 Notes:
R: rumen
G: glandular part
R + G: sum of R and G
A1: reference composition with the following formulation for 100 g:

- colloidal aluminum phosphate	55	g
- methyl para-hydroxybenzoate	0.11	g
- propyl para-hydroxybenzoate	0.04	g
- sorbic acid	0.15	g
- saccharose	15	g
- other excipients: pectin, agar-agar, orange essence and water, q.s.p.	100	g

A2: reference composition described in the above-mentioned Dictionnaire Vidal and having the following formulation for 100 g (powder presentation):

- $NaHCO_3$	52 g
- $CaCO_3$	41 g
- $Ca_3(PO_4)_2$	2 g
- $Mg(OH)_2$	3 g
- TiO_2	2 g

A3: comparative example

[Commas between numbers indicate decimal points.]

Claims

1. Therapeutical composition useful as digestive tract, comprising as active ingredient mineral substances, and endowed with coating and thixotropic properties, characterized in that it contains, in association with a physiologically acceptable excipient, at least two mineral substances:

A - titanium oxide as coating and thixotropic means in suspension, and
B - an antacid means, selected from the group constituted by $CaCO_3$, MgO, aluminium phosphate, Al_2O_3, $Al(OH)_3$, $MgCO_3$ and $BaCO_2$,

the weight ratio A-B being between (1:10) and (10:1), and the content of means A being greater than or equal to 5% by weight with respect to the weight of said composition.

2. Composition according to claim 1, characterized in that in addition to means A and B, it contains a means C promoting the intestinal transit and selected from the group constituted by clay, bentonite and montmorillonite, the weight ratio C-A being between (1:90) and (1:10) and advantageously between (1:50) and (1:20).

3. Composition according to claim 1, characterized in that, in addition to means A and B, it contains a gelling means D, selected from pectine and cellulose derivatives, the weight ratio D-A being between (1:50) and (1:20).

4. Composition according to claim 1, characterized in that it contains:

A - titanium oxide at a concentration greater than or equal to 5% by weight with respect to the weight of said composition,
B - an antacid means, selected from the group constituted by $CaCO_3$, MgO, aluminium phosphate, Al_2O_3, $Al(OH)_3$, $MgCO_3$ and $BaCO_3$, the weight ratio A-B being between (1:10) and (10:1), and preferably between (1:1) and (10:1),
C - a means promoting intestinal transit selected from the group constituted by clay, bentonite and montmorillonite, the weight ratio C-A being between (1:50) and (1:20), and
D - a gelling means selected from the group constituted by pectine and carboxymethylcellulose, the weight ratio D-A being between (1:50) and (1:20).

5. Composition according to claim 4,

characterized in that it contains, in percentage by weight with respect to the weight of said composition, 9% of TiO_2, 3% of $CaCO_3$, 0.25% of clay and 0.30% of carboxymethylcellulose.